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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,745	02/28/2002	Gary de Jong	24601-416C	8781

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EXAMINER	
LAMBERTSON, DAVID A	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 08/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,745	DE JONG ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-22,31,33 and 35-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *18-22 and 35-41* is/are allowed.

6)☒ Claim(s) *17,31 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed May 26, 2005. Amendments were made to the claims.

Claims 17-22, 31, 33 and 35-41 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, mailed January 6, 2005, that is not addressed in this action has been withdrawn.

Because this Office Action only maintains rejections set forth in the previous Office Action and/or sets forth new rejections that are necessitated by amendment, this Office Action is made FINAL.

Information Disclosure Statement

The information disclosure statement filed June 10, 2005 has been considered, and a signed and initialed copy of the form PTO-1449 is attached to this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17, 31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nolan in view of Neves (as recited previously). **This rejection is maintained for the reasons set forth in the previous Office Action.**

Response to Arguments Concerning Claim Rejections - 35 USC § 103

Applicant's arguments filed May 26, 2005 have been fully considered but they are not persuasive. Applicant provides the following grounds of traversal:

1. Applicant argues that nowhere does Nolan teach or suggest labeling the chromosome prior to treating the cells, but rather merely exemplifies labeling the chromosome subsequent to its entry into the cell by using A3 and Hoechst 33258, which are dyes for staining chromosomes post-introduction into a cell (see for example pages 7-8 of Applicant's response).

2. Applicant argues that Neves does not remedy the lack of a teaching for the labeling of a "large" nucleic acid prior to introduction into a cell because they merely teach that their labeling method can be used for "small" nucleic acids such as plasmids (see for example page 7 and 9 of Applicant's response). For example, Applicant states that Neves does not disclose how their method would be applicable to "large" nucleic acids, or how to purify the "large" nucleic acids after they had been labeled (see for example page 10 of Applicant's response).

3. Applicant argues that the Examiner has provided no evidence to suggest that one of ordinary skill in the art would have a reasonable expectation of success when combining the teachings of Nolan and Neves, and instead has relied on the instant specification as a guide for combining the teachings (see for example the bridging paragraph of pages 8-9 of Applicant's arguments).

4. Applicant argues that the Office has misinterpreted the standard for establishing a *prima facie* case of obviousness by stating "there is no reason to expect that one of ordinary skill in the art could not fluorescently label a chromosome using the method taught by Neves." Applicant argues that this does not establish a reasonable expectation of success because there is no

statement in either Neves or Nolan suggesting that the methods are compatible (see for example page 9 of Applicant's response).

5. Applicant argues that there would further be no expectation of success because (1) Neves teaches that linear DNA molecules are sensitive to DNases, thereby resulting in the detection of free nucleotides as opposed to large nucleic acids and (2) one of the methods taught by Nolan (using a laser to transfect cells with a large DNA molecule) would be incompatible with the label used by Neves (see for example pages 10-11 of Applicant's response).

Applicant's arguments have been considered but are not found persuasive for the following reasons:

1. It is reiterated that Nolan teaches the use of a chromosome that is labeled; this is clear from the bridging paragraph from pages 9-10 of Nolan. Applicant's argument is that this statement only refers to labeling a chromosome after it is introduced into the cell. However, nowhere in this section is it specifically stated by Nolan that the labeling must occur post-introduction. Indeed, Nolan specifically states that various modifications and variations can be made to the invention (see for example page 14 of Nolan). Thus, not only does Nolan not exclude labeling a chromosome prior to its introduction into a chromosome, Nolan specifically states that variations of their method are contemplated.

Applicant's sole support for their argument is that in each example, Nolan only uses post-introduction labeling of their chromosomes. However, it is improper to limit the teachings of Nolan to their examples, especially in light of their explicit statement that variations and modifications of their method are contemplated. Given that Nolan teaches using *any*

fluorescently labeled chromosome, and Neves teaches that DNA can be fluorescently labeled, the ordinary skilled artisan would recognize that a pre-labeled chromosome would be an obvious variation within the scope of variations contemplated by Nolan.

2. A DNA molecule is a DNA molecule, regardless of its size. Thus, it is unclear why Applicant believes the method taught by Neves for labeling a DNA molecule would not be applicable to the DNA molecule used in Nolan. There is no explanation provided for Applicant's position that a "small" DNA molecule can be labeled by the method taught by Neves, but a "large" DNA molecule cannot be labeled by the same method. The molecules are chemically the same, made up of a polymer of nucleic acids; the mechanism for labeling the "small" DNA is a chemical reaction that takes advantage of the chemical properties of a polynucleotide- this is regardless of the length (i.e., size) of the nucleic acid molecule. There is no logical or scientific evidence to support Applicant's allegation that procedures for the labeling and purification of a "large" DNA molecule are different than procedures for the labeling and purification of a "small" DNA molecule. Indeed, this would merely appear to be a "scaling up" in the size of the molecule used in a procedure. However, According to MPEP § 2144.04 (IV)(A) (In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)) "mere scaling up of a prior art process capable of being scaled up, if such were the case, would not establish patentability in a claim to an old process so scaled." 531 F.2d at 1053, 189 USPQ at 148. Thus, it is clear that by teaching a method for labeling a "small" nucleic acid sequence, Neves teaches a method of labeling *any* nucleic acid, regardless of its size, absent some evidence that there are only certain labeling procedures that can be performed on "large" nucleic acids, and that these do not overlap with the procedures for labeling "small" nucleic acid sequences.

3. The Office has not relied on the instant specification to combine the teachings of Neves and Nolan to arrive at the instantly claimed invention. As set forth in the previous Office Action, Nolan teaches a method of transfecting an artificial chromosome into a host cell, wherein the chromosome is preferably fluorescently labeled. Neves teaches a method for labeling a nucleic acid prior to transfecting it into a host cell. One of ordinary skill in the art would clearly recognize that, in order to use a fluorescently labeled nucleic acid in the method of Nolan, one would first need to make a fluorescently labeled nucleic acid; Neves teaches such a method. Thus, it would be obvious for the skilled artisan to combine the teachings of Nolan and Neves in order to fluorescently label a nucleic acid to be used in the method of Nolan. Therefore, the evidence for combining the teachings of Nolan and Neves comes from the references alone, and does not require using the instant specification as a guide, as suggested by Applicant.

4. The Office has not misinterpreted the standard for establishing a reasonable expectation of success in making a *prima facie* case of obviousness. The statement "there is no reason to expect that one of ordinary skill in the art could not fluorescently label a chromosome using the method taught by Neves" establishes a reasonable expectation of success because there is no reason to think a method for labeling a plasmid would be inoperable on a larger nucleic acid. Again, this is simply a "scaling up" of the procedure; the "large" nucleic acid and "small" nucleic acid are chemically the same, being comprised of nucleic acid sequences. Thus, a method that labels nucleic acid sequences will work on "large" and "small" nucleic acids, absent some teaching that indicates labeling techniques for "small" nucleic acids do not work on "large" nucleic acids.

As it regards Applicant's argument that there is no statement in Neves or Nolan to indicate that the methods are compatible, it is submitted that there is no statement in the art at the

time of filing, let alone Neves and Nolan, indicating that the methods are *incompatible.* Since the Office as provided adequate obviousness, motivation and expectation of success statements, the burden is on Applicant to provide evidence as to why one of ordinary skill in the art could or would not combine the teachings of Neves and Nolan. However, simply arguing that there is no direct statement saying the references can be combined is not evidence that the references *cannot* be combined, especially in light of the statements provided by the Office.

5. First, the fact that Neves teaches that linear molecules are more sensitive to DNases does not lower the expectation of success when using their method. According to Neves, DNases will affect DNA molecules that have been labeled by nick translation methods that result in relaxation of the plasmid (see for example the left column, second paragraph of page 51); as indicated on pages 52-53, Neves uses a photoactivation method to label their nucleic acids, to specifically avoid making the nucleic acids susceptible to DNases (see also the left column of page 51 of Neves). Thus, this argument is not convincing as to a lack of an expectation of success. Second, Nolan uses more than a laser-mediated method for transfecting chromosomes into a cell; they also use electrically induces transfusion and linear accelerators to introduce the chromosomes into cells. These techniques will have no affect on the labeled chromosomes, thus there is no incompatibility between the methods of Nolan and Neves.

In conclusion, Applicant provides their traversal on two primary grounds: (1) that Nolan does not teach a method for introducing a labeled chromosome into a cell, but merely the labeling of a chromosome that has been introduced into a cell; and (2) that there would be no expectation of success labeling a "large" nucleic acid based on a method for labeling of a "small" nucleic acid. However, these grounds are not convincing, as presented above.

Nolan clearly indicates that there method preferably uses any fluorescently labeled chromosome, and this necessarily encompasses chromosomes that are labeled prior to their introduction into a cell since there is no exclusion of such a process. Furthermore, it is improper to limit Nolan to merely their examples, especially when Nolan clearly indicates that they contemplate obvious variations. Additionally, one cannot simply consider the teachings of Nolan without the teachings of Neves in this instance, because if Nolan explicitly (instead of implicitly) taught the labeling of a chromosome prior to its introduction into a host cell, then there would be no need for an "obviousness-type" rejection as the reference would be anticipatory. As set forth previously, the combined teachings of Neves and Nolan teach a method for using a chromosome that has been fluorescently labeled prior to its introduction into a host cell, thereby making the instantly rejected claims obvious.

Furthermore, Applicant provides no scientific explanation as to why the method used by Neves would not be suitable for labeling a "large" nucleic acid. The method works on a "small" nucleic acid, which has the same chemical composition as a "large" nucleic acid: both are made of a polymer of nucleic acids. The only difference is that the "large" nucleic acid has a longer sequence than the "small" nucleic acid. The method of labeling a "small" nucleic acid taught by Neves would simply be performed on a longer nucleic acid, with the same expectation of success due to the chemical nature of the molecule, and the chemical reaction (photoactivation) used to label the molecule. The argument of "susceptibility to DNases" is moot, as photoactivation has not been taught to make molecules more susceptible to DNases, and this is in fact why Neves uses such a method. Furthermore, the inability to use a "laser-mediated" approach to introducing a chromosome into a cell does not preclude the combination of Neves and Nolan, as Nolan

clearly teaches other methods of introducing chromosomes into cells. Absent some evidence that not all labeling methods will work on "large" nucleic acids as opposed to "small" nucleic acids, the ordinary skilled artisan would have had obviousness, motivation and an expectation of success when combining Neves and Nolan, as provided in the previous Office Action. As such, the instant claims are obvious in view of such teachings, and the rejection is maintained.

Allowable Subject Matter

Claims 18-22 and 35-41 are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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JAMES KETTER
PRIMARY EXAMINER